Improved Procedure for the Solution Phase Preparation of 1,4-Benzodiazepine-2,5-dione Libraries via Armstrong's Convertible Isonitrile and the Ugi Reaction

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Introduction

Reports of the biological utility of 1,4-benzodiazepine-2,5-diones (BDP's) have appeared in several areas, including applications as antagonists of the platelet glycoprotein IIb-IIIa[1] and anticonvulsant agents.[2] This note reports an improved procedure for production of high-yielding BDP solution phase libraries in a 96-well plate format based on a two-step synthesis of this template recently reported by Armstrong and Keating.[3] The literature synthesis employs the Ugi MCR[4] using anthranilic acids and 1-isocyanocyclohexene (Armstrong's convertible isonitrile)[5] as the acid and isonitrile inputs, respectively. Subsequent acid-catalyzed cyclization of the anthranilic amine (the so-called "internal nucleophile") produces the desired BDP, with reported isolated yields for the two-step procedure ranging from 15 to 50%.[6] We envisaged that such yields would not be sufficient for extension to production of high-quality/-purity solution phase libraries. An alternative protocol was therefore developed by employing *N*-BOC-protected anthranilic acids, Scheme 1.

Results and Discussion

It was thought that protection of the anthranilic nitrogen could prevent competing and undesired participation in the Ugi reaction, a potential explanation for the moderate yields reported for the parent synthetic route.[6] BOC removal and cyclization to BDP could both sequentially be achieved on treatment with acid in "1 pot", in an analogous fashion to the strategy employed in this laboratory for the solution phase synthesis of

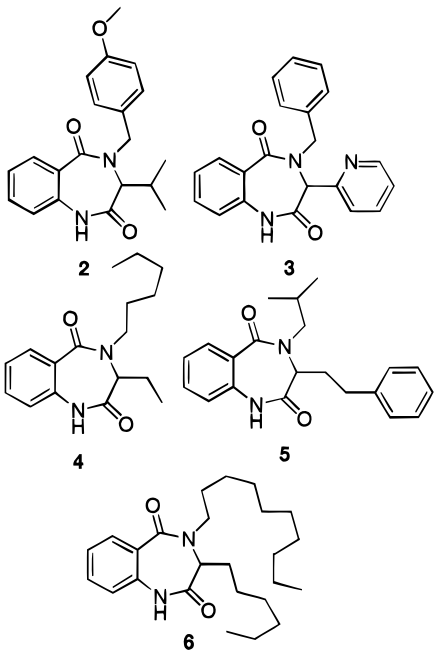
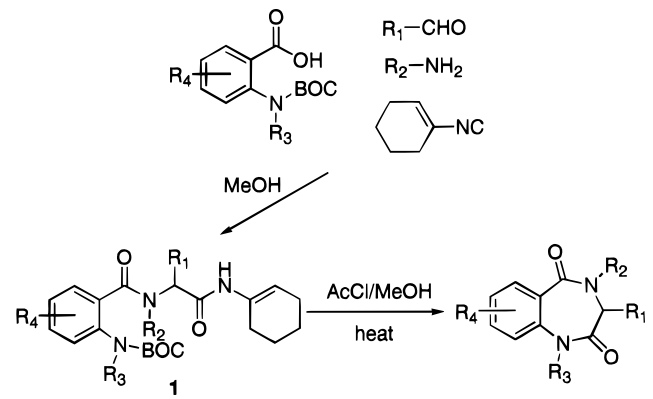


Figure 1.

Scheme 1



diketopiperazines.[7] Syntheses of five BDP's, designated **2**−**6**, Figure 1, were evaluated to compare the relative merits of the *N*-BOC-protected anthranilic acid (R = BOC) route as opposed to the literature route employing unprotected anthranilic acid (R = H). A simplified experimental procedure was followed by adding each reagent in order of its participation in the Ugi reaction mechanism. Equal amounts (0.1 mL) of 0.1 M solutions of the four components were employed generating a theoretical 10 μmol of final BDP product (for 100% conversion). The 4-component condensation was performed in methanol at room temperature and the solvent evaporated at 65 °C.[8] The deprotection/cyclization steps were performed using either a 10% solution of acetyl chloride in methanol, procedure I, or a 10% solution of TFA in dichloroethane, procedure II. Solvents were then evaporated at 65 °C. Both area % (*A* %) yields (measured by LC/MS, detector UV 220 nm, *A*% defined as HPLC

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(8) Performed in a SAVANT evaporator for 2 h at 65 °C.

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Table 1

	R = H		R = BOC			
entry	area % I[a]	isol % I[b]	area % I[c]	area % I[d]	isol % I[e]	area % II[f]
2	35	52	77	87	81	84
3	17	15	54	36	32	49
4	29	25	90	56	42	84
5	40	26	98	83	79	87
6	35	9	66	79	65	48

[a] R = H, area % I = area % yields for procedure I (10% AcCl/MeOH) with anthranilic acid (R = H). [b] R = H, isol % I = isolated yields reported by Armstrong et al. for procedure I with anthranilic acid (R = H).[6] [c] R = BOC, area % I = area % yields for procedure I (10% AcCl/MeOH) with *N*-BOC anthranilic acid (R = BOC). [d] R = BOC, area % I = area % yields for procedure I (10% AcCl/MeOH) with *N*-BOC anthranilic acid (R = BOC), scaled up. [e] R = BOC, isol % I = isolated yields for procedure I (10% AcCl/MeOH) with *N*-BOC anthranilic acid (R = BOC), scaled up. [f] R = BOC, area % II = area % yields for procedure II (10% TFA/DCE) with *N*-BOC anthranilic acid (R = BOC).

integrated area under the curve) and isolated yields from a scaled procedure of BDP are reported in Table 1.

Area % yields of BDP (17−40%) closely parallel the isolated yields reported by Armstrong[5] when using anthranilic acid (R = H) and the AcCl/MeOH reagent combination. A large number of side products are observed on HPLC analysis of the final crude material, as can be seen in Figure 3 of BDP **5**. LC/MS yields of the intermediate Ugi product containing the convertible isonitrile were difficult to determine due to decomposition on exposure to HPLC elution conditions. An analogous Ugi reaction with cyclohexylisocyanide, which produces a more stable Ugi product, showed substantial side product formation during the Ugi condensation with anthranilic acid. The same reaction with *N*-BOC anthranilic acid as the acid component gave 4−5-fold higher LC/MS *A* % yields suggesting that the source of side products is due to side reactions involving the free anthranilic amine.[9] This is further substantiated by the dramatic increases in both *A* % and isolated yields of BDP with *N*-BOC anthranilic acids, exemplified by the virtually clean HPLC analysis, Figure 2, of BDP **5**. Similar 2−3-fold improvements in *A* % yield are observed for BDP's **2**−**4** and **6**. The reaction is also amenable to scale-up with isolated yields similar to *A* % yields. ^{1}H NMR of BDP's **2**−**6** were in agreement with those reported by Armstrong.[5,6] Treatment of the intermediate *N*-BOC Ugi product **1** with 10% TFA in dichloroethane also produced comparable high yielding conversions to the desired seven-membered ring cyclized material. In agreement with literature reports when using the AcCl/MeOH reagent combination, intermediate methyl esters were not detected during reaction implying rapid cyclization of these compounds to BDP. Encouraged with the improved yields of benzodiazepine-2,5-dione using *N*-BOC anthranilic acid, the chemistry was advanced to production in a 96-well format. Reagents in a 1 (*N*-BOC anthranilic acid) × 8 (R_1CHO) × 12 (R_2NH_2) × 1 (1-isocyanocyclohexene) format were transferred to a 96-well plate using a Quadra 96 (Tom tech) dispensing system. The LC/MS *A* % yields taken from two 96-well plates utilizing this chemistry are presented in Table 2, along with the participating reagents, Figure 4. The desired molecular ion was detected in every well. The first percentage corresponds to *A* % yields with *N*-BOC anthranilic acid **7**, and the second percentage is for the *N*-methylated analogue **8**, Scheme 1. The reaction is general for both a range of commercially available aldehydes [e.g. aldehydes with attached ester, heteroaryl, aryl, amido, thioalkyl, alkyl, and cycloalkyl functionality; for example, aldehydes **21** through **28**] and primary amines [e.g. with attached alkyl, aryl, heteroaryl, acidic

(9) *A* % yield of Ugi product: *N*-BOC anthranilic acid, 85%, and anthranilic acid, 15%, with isobutylamine, phenylpropionaldehyde, and cyclohexylisocyanide as supporting reagents.

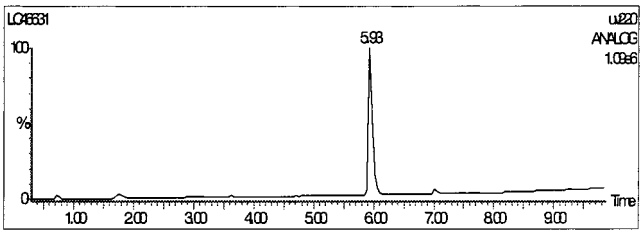

Figure 2.

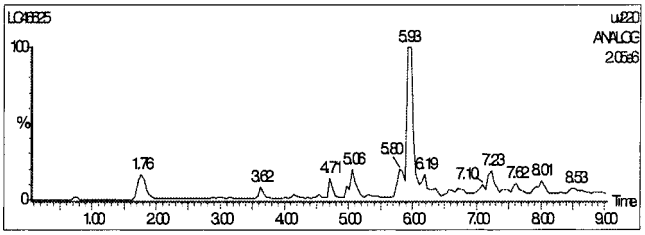

Figure 3.

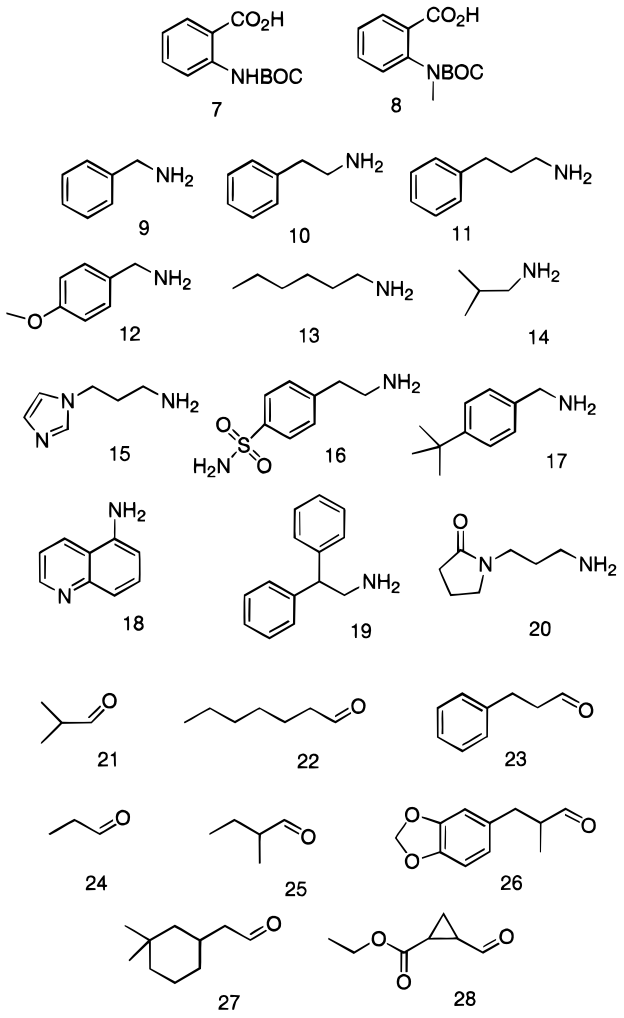

Figure 4.

Table 2[a]

	9	10	11	12	13	14	15	16	17	18	19	20
21	40/16	40/29	40/27	54/15	40/25	39/40	26/16	18/21	41/15	0/0	39/31	47/30
22	85/87	82/72	77/64	79/72	82/69	84/67	81/73	78/67	82/74	43/10	88/74	84/73
23	88/84	85/73	89/68	92/81	92/78	88/68	90/75	82/73	84/79	39/8	76/77	85/72
24	87/80	72/52	69/43	79/70	70/41	80/51	87/63	81/64	81/70	51/25	75/60	80/62
25	45/10	37/24	39/22	36/12	34/20	33/12	41/7	28/26	44/10	9/0	37/16	39/20
26	79/49	74/61	63/51	75/12	66/53	69/54	59/10	74/61	83/67	6/0	71/49	67/64
27	89/87	86/69	88/66	85/82	89/63	85/70	90/74	83/69	86/84	38/8	84/74	88/78
28	85/64	86/63	80/67	85/82	84/75	85/64	82/69	84/67	86/75	27/11	84/69	83/61

[a] Note: For *A* % yields *x*/*y*, the first yield *x* represents that for reactions with *N*-BOC anthranilic acid, **7**. The second yield *y* represents that for *N*-Me-BOC anthranilic acid, **8**. Row **21** represents yields of reactions with aldehyde **21**. Column **9** represents yields of reactions with amine **9**.

and basic functionality; for example, amines **9** through **20**]. The process is also viable, albeit lower yielding, for *N*-methylated-BOC anthranilic acids. Lowest *A* % yields in both plates corresponded to wells containing the two branched aliphatic aldehydes, **21** and **25**, and 5-aminoquinoline, **18**.

In summary, an improved high-yielding solution phase synthesis of 1,4-benzodiazepine-2,5-diones has been reported. The *N*-BOC protection strategy of anthranilic acids and their reaction in the Ugi condensation followed by "1 pot" deprotection and cyclization to BDP is amenable to both scale-up and solution phase library synthesis in a 96-well plate format. The facile production protocol of this approach, coupled with high yields, provides a realistic and complementary solution phase alternative to several solid-phase syntheses of 1,4-benzodiazepine-2,5-diones reported recently.[10]

Experimental Section

Reagents were obtained from commercial sources and used as received. *N*-BOC anthranilic acid (**7**) was purchased from Advanced Chem-tech, and *N*-BOC-methyl anthranilic acid (**8**) was purchased from Aldrich. Proton nuclear magnetic resonance (^{1}H NMR) spectra were run at 500 MHz. LC/MS analysis was performed using a C18 Hypersil BDS 3μ 2.1 × 50 mm column (UV 220 nm) with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 5 or 15 min. HPLC was interfaced with APCI techniques.

Typical Experimental Procedure (Plate Production). Stoichiometric amounts (0.1 mL) of 0.1 M solutions of the four Ugi components in methanol were combined in order of their participation in the Ugi reaction (aldehyde first, amine second, isonitrile third, and the carboxylic acid fourth) and shaken at room temperature for 20 h. The reagents were dispensed into the 96-well plate using a QUADRA 96 (Tom tech) multidispensing system. The solvent was then evaporated in vacuo in a SAVANT evaporator at 65 °C for 2 h. The Ugi products were then treated with a 10% AcCl/MeOH solution (400 μL/well) and shaken overnight at room temperature. The solvent was then removed in vacuo at 65 °C with a SAVANT evaporator for 2 h. LC/MS analyses were performed on every well, and *A* % yields of the desired product are reported in Table 2.

Typical Experimental Procedure (Scale-Up). Stoichiometric amounts (1.75 mL) of 0.1 M solutions of the four Ugi components were combined in order of their participation in the Ugi reaction and stirred at room temperature for 20 h. The solvent was evaporated in vacuo at 40 °C and dried under high vacuum. A 10% solution of AcCl in MeOH (7 mL) was added to the crude material and stirred at room temperature for 15 h. The solvent was then evaporated in vacuo at 40 °C. The crude material was preabsorbed onto flash silica and purified by flash column chromatography (EtOAc/hexane) to yield the desired product. The following benzodiazepines were prepared via this procedure.

(*R*,*S*)-3-Isopropyl-4-(4-methoxybenzyl)-1,4-benzodiazepine-2,5-dione (2). See scale-up general procedure, isolated yield 81%. Data for major diastereomer only: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 8.9 (s, 1H), 7.99−8.01 (m,1H), 7.41−7.45 (m, 1H), 7.31−7.33 (m, 2H), 7.21−7.24 (m, 1H), 6.85−6.89 (m, 1H), 6.82−6.84 (m, 2H), 5.14−5.17 (m, 1H), 4.44−4.47 (m, 1H), 3.74 (s, 3H), 3.62−3.65 (m, 1H), 1.65−1.70 (m, 1H), 0.82−0.83 (m, 3H), 0.66−0.67 (m, 3H). Data for both diastereomers: ^{13}C (125 MHz, $CDCl_3$, ppm) 172.2, 166.3, 159.5, 134.9, 132.8, 131.7, 130.4, 128.8, 127.0, 125.0, 120.0, 114.2, 71.3, 55.4, 54.9, 27.8, 19.8, 19.6.

(*R*,*S*)-4-Benzyl-3-(2-pyridyl)-1,4-benzodiazepine-2,5-dione (3). See scale-up general procedure, isolated yield 32% of a 10:1 mixture of conformers. Data for major diastereomer only: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 8.68 (1H, br s), 8.19−8.20 (1H, m), 7.68−7.70 (1H, m), 7.53−7.55 (2H, m), 7.26−7.36 (4H, m), 7.14−7.17 (1H, m), 6.93−6.96 (1H, m), 6.86−6.89 (1H, m), 6.73−6.77 (1H, m). Data for major diastereomer only: ^{13}C (125 MHz, $CDCl_3$, ppm) 171.5, 167.2, 154.0, 148.7, 136.4, 136.2, 134.7, 132.1, 131.0, 129.2, 128.9, 128.2, 127.2, 124.5, 122.4, 120.2, 119.6.

(*R*,*S*)-3-Ethyl-4-hexyl-1,4-benzodiazepine-2,5-dione (4). See scale-up general procedure, isolated yield 42% of a 2:1 mixture of conformers. Data for major diastereomer only: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 0.80−0.98 (6H, m), 1.20−1.30 (6H, m), 1.50−1.70 (4H, m), 3.25−3.35 (1H, m), 3.90−3.94 (1H, m), 4.00−4.10 (1H, m), 6.90−6.95 (1H, m), 7.2−7.25 (1H, m), 7.40−7.5 (1H, m), 7.90−7.96 (1H, m), 8.60 (1H, br s). Data for both diastereomers: ^{13}C (125 MHz, $CDCl_3$, ppm) 172.4, 172, 171.7, 168.2, 165.6, 135.6, 134.49, 132.3, 132.1, 131.7, 131.4, 128.0, 127.1, 125.2, 124.8, 120.3, 119.7, 66.5, 57.0, 52.3, 51.7, 42.5, 31.5, 28.6, 28.0, 26.6, 26.4, 22.7, 22.5, 19.6, 14.0, 11.2, 10.8.

(*R*,*S*)-4-Isobutyl-3-(2-phenylethyl)-1,4-benzodiazepine-2,5-dione (5). See scale-up general procedure, isolated yield 79% of a 2:1 mixture of conformers. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 0.88−0.89 (3H, m), 0.93−0.94 (3H, m), 1.70−1.78 (1H, m), 1.85−1.90 (1H, m), 1.91−2.00 (1H, m), 2.50−2.62 (2H, m), 2.90−2.93 (1H, m), 3.96−4.04 (2H, m), 6.98−7.01 (2H, m), 7.1−7.3 (5H, m), 7.4−7.45 (1H, m), 7.95−8.0 (1H, m), 8.78(1H, s). Data for both diastereomers: ^{13}C (125 MHz, $CDCl_3$, ppm) 172.3, 171.8, 168.5, 166.0, 140.4, 139.7, 135.6, 134.5, 132.5, 132.2, 131.7, 131.6, 128.5, 128.5, 128.4, 128.3, 128.3, 127.7, 127.0, 126.4, 126.4, 126.2, 125.2, 125.0, 120.3, 119.8, 117.3.

(*R*,*S*)-3-hexyl-4-decyl-1,4-benzodiazepine-2,5-dione (6). See scale-up general procedure, isolated yield 65% of a 2:1 mixture of conformers. Data for major diastereomer only: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 8.84 (1H, br s), 7.93−7.96 (1H, m), 7.41−7.45 (1H, m), 7.21−7.27 (1H, m), 6.95−6.99 (1H, m), 3.98−4.04 (2H, 2 × m), 3.29−3.33 (1H, m), 1.09−1.32 (26H, m), 0.87−0.89 (6H, m). Data for both diastereomers: ^{13}C (125 MHz, $CDCl_3$, ppm) 172.7, 172.2, 171.9, 168.2, 165.7, 135.6, 134.6, 132.3, 132.1, 131.6, 131.4, 130.3, 127.9, 127.1, 125.1, 124.8, 120.3, 119.7, 117.4, 116.3, 65.1, 55.6, 52.3, 51.7, 42.6, 31.9, 31.6, 31.5, 31.3, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.6, 28.5, 28.1, 27.0, 26.8, 26.6, 26.3, 26.1, 22.7, 22.6, 22.5, 22.4, 14.1, 14.0, 14.0, 13.9.

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